The clinical use of MEG activity associated with brain lesions

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1 Introduction

Brain lesions may alter the surrounding brain tissue structurally by moving or compressing it, or by infiltration or edema. Electrophysiological signs of the deteriorated function in these border zones can be focal slow (and fast) wave and epileptic activity in MEG (and EEG).

Clinically it is of great interest to know the localization and the extent of these focal sources, but also the location and the extent of the evoked and event related activity of functionally important areas around brain lesions. So we developed, adapted and established clinical applications in neurosurgery and neurology with special reference to clinical relevance and acceptance.

2 Methods

2.1 Magnetic Source Imaging (MSI)

2.1.1 Biomagnetic recording and source localization: From 1990 to 1994 we used the 37 channel system "Krenikon^R" of Siemens, Erlangen, Germany (planar recording surface of 20 cm in diameter), and since 1995 the 2x37 channel system "MAGNES II^R" of Biomagnetic Technologies Inc. (BTi), San Diego, CA, USA, (curved recording surface with a 14 cm open diameter). The transfer of the coordinates from the head to the recording device and to the magnetic resonance imaging (MRI) data set was done with our surface fit (edge detection algorithm) of the electrically measured head surface (Isotrack^{TM} 3D-digitizer, Polhemus Navigation Sciences, Colchester, Vermont, USA) and the head surface which was reconstructed from the MR images. The transfer error is less than 2 mm. The advantages are: (1) easy scanning of the head surface, (2) no need of fiducial points [19].

We used the sphere as the volume conductor model [22]. The source model was - depending on the task - either the single current dipole model or a current distribution solution. In order to apply the single current dipole model in a more adequate way, the localization procedure is performed only on signal sections where one component predominantly describes the signal. The principle component analysis (PCA) is used to select typically only 1-2 % of the whole recording signal, speeding up the source localization procedure substantially [18].

2.1.2 MEG multisource problem: The electric or magnetic fields of brain activity not only originate from the sources of interest but also from the rest of the brain. In order to reduce this "background activity" we use besides the alpha blocking effect during the recording (eyes open) either one of two procedures:

Following the localization of dipoles we use a spatial averaging, our Dipole-Density-Plot (DDP), which shows the spatial distribution of dipoles over the recording time. It works by a three dimensional convolution using a three dimensional Gaussian envelope, that takes into account the localization uncertainty [18,38].

Or we use a current density procedure, the CLSF (Current Localization by Spatial Filtering), which we adapted from Robinson and Rose [32]. Our analyzing space (a sphere) consists of 7000 voxels which is adjusted in size and location to the area of interest [10]. The Current-Density-Plot (CDP) is our corresponding spatial averaging of the CLSF [13].

2.2 Functional Magnetic Resonance Imaging (fMRI) and Magnetic Resonance Spectroscopic Imaging (MRSI)

For details of these comparing methods see for the fMRI, (^{1}H MRSI) in [35], and for the MRSI in [16].

3 Results and Discussion

3.1 Clinical Applications: Normal activity

The tool to localize the spatial relation of tumors and their border zones to the cortical somatosensory, motor, auditory and cortical speech areas are now routinely used in Erlangen for operation planning and intraoperative functional neuronavigation with either the Zeiss microscope neuronavigation system (MKM), or the Stealth pointer neuronavigation system [7].

3.1.1 Somatosensory evoked and motor event related responses: In neurosurgery the clinical usefulness of the somatosensory magnetic evoked responses (SEF = somatosensory evoked field) have been demonstrated [5,9,17,25,26,30,36]. A coupling of MSI results to the neuronavigator in image guided neurosurgery was also described [31,43]. The first motor related MEG response was the so called "Bereitschaftsfeld" of the supplementary motor area [4]. The localization of the directly motor induced MEG activity (MEF = motor evoked field) in the precentral gyrus followed [21].

Up to June 2000 we localized in 137 patients with tumors around the central sulcus successfully the somatosensory response in 131 cases (95,6 %) and the motor associated cortical responses in 68 out of 72 cases (94,4%), elicited by selfpaced finger movements (trigger obtained by rectified electromyogram). The SEF-MEG results coincided in all patients with the intraoperatively evoked phase reversal of the epicortically obtained evoked potentials [7,8,9].

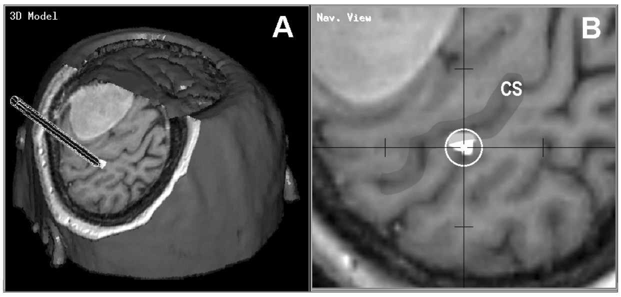

Figure1: *Single dipole MSI source localization in the postcentral gyrus using the somatosensory evoked field (SEF) at 50 ms after the tactile stimulus of the right index finger (200 samples averaged) of a 65 years old female patient (wwa) with a meningeoma. A: display of the Stealth neuronavigator showing in a tangential plane the tumor and the MSI SEF source and the intraoperatively used pointer instrument. B: enlarged section of A, the central sulcus is shaded, and marked by CS and the SEF source by a white encircled spot (from [37]).*

86 patients out of the 137 patients were operated by using the functional neuronavigation. 26 patients have not been operated on the basis of the MSI findings. In figure 1 an example is shown of the SEF dipole source in the postcentral gyrus in a patient with a meningeoma displayed by the Stealth neuronavigator system (c.f. [7,8,9]).
Figure 2 shows in a patient with a left astrocytoma an example of the MEF and the SEF dipole sources in the pre- and post-central gyrus respectively.

3.1.2 MSI and functional MRI (fMRI): The "blood oxygenation level dependent contrast" (BOLD) [28] enables the functional magnetic resonance imaging (fMRI) [1], which is used to localize oxygenation differences caused by evoked or event related brain activity. Some fundamental differences between the MSI and the fMRI may result in misinterpretations of the fMRI localization results. One of these is the different origin of the recorded signals: In MSI the neuronal areas will be localized. But In fMRI the venous branch of the blood supply indicates the oxygen level change [28,33]. Another important difference is the time resolution: In fMRI it is in the order of seconds depending on the tissue diffusion and regulation time of oxygen. In MSI the time resolution is in the order of a millisecond. depending on the electric properties of the tissue and the recording equipment. So fMRI interpretations should be done with general caution.

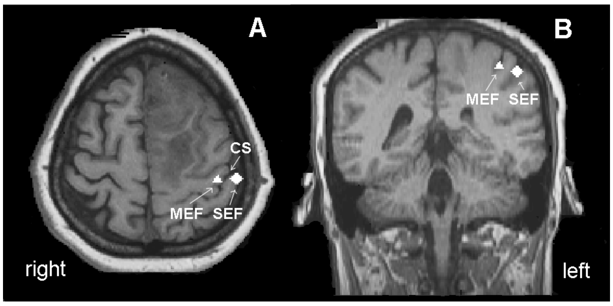

Figure 2: *Single dipole MSI source localizations of the motor related source (MEF) in the precentral and of the somatosensory evoked field (SEF) in the postcentral gyrus of a 39 years old female patient (age) with a left astrocytoma. SEF and MEF dipole sources are marked respectively. The central sulcus is marked by CS in A. The SEF protocol was as in figure 1. The MEF source was localized at 100 ms after the movement onset of selfpaced brisk movements of the right index finger (100 samples averaged) (from [37]).*

The consequence of the two different principles of the signal origin is demonstrated in our two comparing studies with 6 subjects [35] and 15 patients [27]. We found a dislocation of the evoked cortical responses obtained by MSI and fMRI typically by around 1 cm.

3.1.3 Event related speech responses: The clinical usefulness to localize the speech activated cortical areas was demonstrated [13,23,24,34]. In our approach - similar to the WADA-Test [42] - we activate visually by written words and pictograms of monosyllabic concrete objects via a glass fiber bundle from outside the shielded room. In addition to the Wernicke area the Broca area can be activated by internally speaking of the prior recognised terms [11]. In order to enhance the average signal of the speech related signals meaningless pictograms were presented in another trial and were subtracted after averaging from the average of the speech related presentation [13,23,24].

In Erlangen up to June 2000 we localized in 44 patients (37 right and 7 left handed) with brain tumors the speech related cortical areas by using our averaging version of the CLSF, the CDP [23,24]. The handedness was determined by the Edinburgh Handedness Inventory [29]. We had a baseline group of 11 healthy subjects. In right handed people one high activity density was in the posterior part of the left superior temporal gyrus (Wernicke area) around 350 ms and with internal speaking in addition in the left inferior frontal gyrus (Broca area) around 500-600 ms (methods c.f. [13]). 12 out of 44 patients suffered preoperatively from transient or permanent speech disturbances.

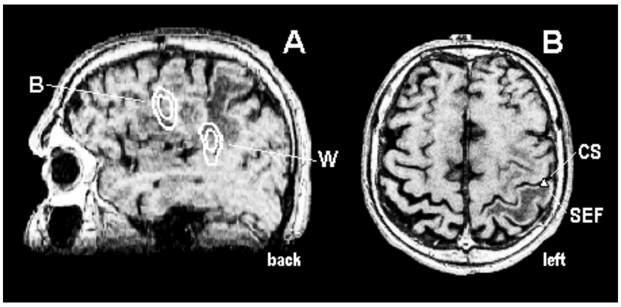

Figure3: *Speech related MSI source localizations in A and somatosensory evoked field (SEF) in B of a 69 years old male patient (jza) with a left temporo-parietal glioma. The speech responses were elicited by presenting pictograms of monosyllabic concrete objects for 800 ms. The task was to recognise the meaning of the object and to speak internally the word of the object. The CLSF was determined of 250 averaged samples and displayed with isocontour lines. The first response appeared 340 ms after the onset of the presentation in the posterior part of the left superior temporal gyrus (Wernicke area) marked by W, and the second response was at 745 ms in the left inferior frontal gyrus (Broca area) marked by B. The SEF protocol was as in figure 1. In B the central sulcus is marked by CS (from [37]).*

In 43 patients (97,7%) the sensory speech area and in 38 patients (86,4%) also the motor speech area could be localized. 24 patients out of the 44 patients were operated. 14 patients were operated by using the functional neuronavigation. None suffered from a postoperative deterioration of speech. 8 patients have not been operated on the basis of the MSI findings [23,24]. Figure 3 shows an example of the localization of the speech areas and the somatosensory evoked responses in a patient with a left temporo-parietal glioma.

The simultaneous recording on both hemispheres allowed to determine the larger activity of the CLSF strength (= S, after regularization) by using the laterality index (LI):

$$\mathrm{LI} = (\text{left } S_{max} - \text{right } S_{max}) / (\text{left } S_{max} + \text{right } S_{max})$$

In 34 of 35 cases the activity was three to nine times larger on the left side and in 1 case three times larger on the right side [23,24]. Figure 4 shows an example of the CLSF hemispheric dominance.
The invasive WADA-test [42] was used for confirmation according to clinical needs restrictively only. In the 5 total cases the test agreed with the LI (4 left side, 1 right side). So this part of the WADA-test might be supplemented or replaced by the MSI approach in the presurgical evaluation of patients. More comparing studies are necessary.

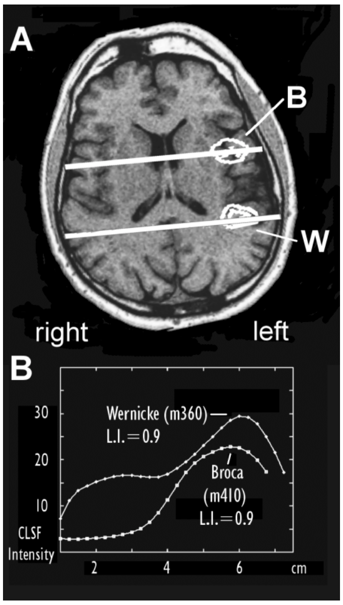

Figure 4: *CLSF-Intensity (used for laterality index (LI)) along lines across the brain at the sensory speech response (W=Wernicke at 360 ms), and at the motor speech response (B=Broca at 410 ms) of a 44 years old male patient with a left temporal low grade glioma. A: test lines and CLSF isocontourlines. B: CLSF- Intensity (after regularization).*

3.2 Clinical Applications: Abnormal activity

3.2.1 Evaluation with structural lesions: The DDP and the CLSF (including the CDP) were tested up to June 2000 in 147 patients in the border zone of tumors and infarcts using focal slow wave activity (2-6 Hz) and in 88 cases using fast wave activity (12.5-30 Hz) [12]. 19 cases were additionally investigated using the magnetic resonance spectroscopy imaging (MRSI). On the basis of our results we can be sure to localize the center and at least the main portion of the functionally impaired area with or without visible lesions in the MRI [15,16,38,40,41].

3.2.2 Epileptogenic lesion: Normally the epileptogenic zone is removed to cure the epilepsy. But the removal of the epileptogenic lesion (assumed to be the original cause of a seizure disorder) is also important for the clinical outcome [3]. Thus the functional localization of the epileptogenic lesion is of great interest. An advantage is: the signals of spontaneous interictal activity are easily to obtain compared to the acquisition of spikes or even a seizure. It appeared, that the spontaneous slow wave activity can be used to localize the epileptogenic lesion of focal epilepsies. [6,21,38,39,40].

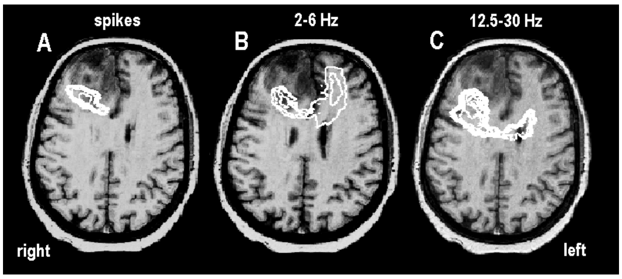

Figure 5: *Current-Density-Plot (CDP) during the 10 minutes recording time of focal abnormal spontaneous interictal activity in the border zone of a right frontal astrocytoma of a 67 years old female patient (ida) with grand mal epileptic seizures. In A: spikes, B: slow (2-6 Hz) and C: fast (12.5-30 Hz) wave activities. In B and C occurring spike/wave activity was eliminated in order to prevent contamination of the slow and fast wave spontaneous activity (from [37]).*

In our studies [39,40] with focal epilepsies we had one group of epileptic patients with structural lesions (5 adults, 4 children) as the reason of the epilepsy, and the other group without any visible structural lesion (4 adults, 2 children). For localization enhancement both the DDP and the CDP have been used. Occurring spike/wave complexes were disregarded in the slow and fast wave activity analysis. The three different signal components (interictal epileptic spikes, slow and fast wave activity) of all patients gave a strong spatial coincidence of the DDP and CDP localizations. In the tumor patients the activity also coincided with the border zone of the tumors [39,40]. Figure 5 shows an example.

Focal abnormal lesional activity even could be found associated with the (focal) Rolandic epilepsy of children [14]. We demonstrated that even in these cases an epileptogenic lesion may be present associated with functional (psychopathological) deficits, in spite of that "per definitionem" no (visible structural) lesion is associated with this disease in the MRI.

So the localization of the epileptogenic lesion seems to be a valuable additional tool in the presurgical evaluation of epileptogenic patients, especially when no structural lesion is visible in the MRI. But more (multicenter) studies should be done to compare the localization of the epileptogenic lesion, interictal spikes and the seizure begin.

3.2.3 Cerebrovascular accidents: Cerebrovascular accidents account for around a quarter of the total mortality and the bulk rate of the disabled people. Therefore it would be of great value to have diagnostic measures for an early detection of prestages.

In our studies we found that the MSI is able to localize not only the disturbed function around an infarct (or tumor) but also that of an area without a visible lesion but with a functional and maybe reversible impairment. These can be either transient ischemic attacks (TIA), or infarcts which are too small to be detected by the standard MRI resolution. Up to now we localized not only the pathological activity associated with brain infarcts in 23 patients, but also in 21 cases the activity associated with the penumbra of transient ischemic attacks (TIA) [16, 20,38,41].

Thus also clinically silent reversible ischemic brain deficits can be localized in accordance to clinically silent brain infarcts [2]. This finding is of clinical importance for the decision, whether an extracranial stenosis of the internal carotid artery has caused deficits or not. And these deficits might be another indication for an endarterectomy [41].

The detection and localization of such clinically silent deficits, caused by a carotid stenosis, needs a screening. So our finding is very helpful, that the abnormal activity of TIAs is lasting at least 4 weeks after the accident [20]. The localization of the penumbra of infarcts is also very important in relation with new therapeutic approaches (i.e. neuroprotectors), that prevent neurons to be damaged irreversibly. More clinical studies should verify the value of these diagnostic tools.

3.2.4 Brain functions and metabolism: The abnormal metabolic function of the brain lesion and the penumbra of infarcts and tumors can be localized by using the proton magnetic resonance spectroscopic imaging (^{1}H MRSI). So we combined the slow wave MSI and the MRSI in order to compare their spatial relation.

3.2.4.1 Brain infarcts: We compared 12 patients with a brain infarct to 12 normal cases using the MEG slow wave dipole density (DDP) and the MRSI signal intensity of *N*-acetyl (NA) (marker for normal function of the brain) and the lactate (Lac) MRSI signal intensity (indicator of anaerobic metabolism) [16]. In the patients at least normal tissue, the border zone, and the bulk of the infarct were included in the analysis.

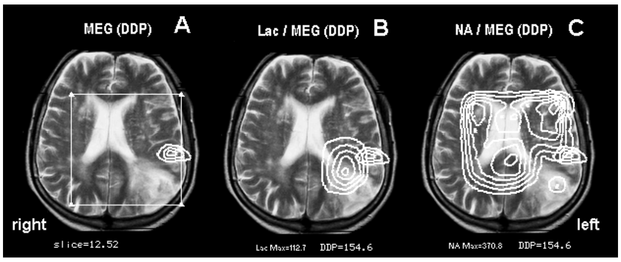

Figure 6: *Dipole-Density-Plot (DDP) of focal abnormal spontaneous slow wave (2-6 Hz) activity of a 60 years old male patient (kfa) during the recording time of 10 minutes in the border zone of a left brain infarct in A. In B and C: additional overlay of a separately recorded proton magnetic resonance spectroscopic imaging (^{1}H MRSI). In B: signals of lactate (Lac); in C: of N-acetyl (NA). Field of view (FOV) 200x200 mm, in A marked by a white line and indicated partly in C by the outer limit of the NA activity; 16x16 phase encoding; nominal in-plane resolution: 12.5 mm, point resolved spectroscopy (PRESS); TR: 1500 ms; TE 135 and 270 ms. Details in [16] (from [37]).*

The signal intensity of NA was significantly reduced in the regions with the highest slow wave activity but was well correlated interindividually with the dipole density (DDP) of the quantified maximum of slow waves. Though Lac was mildly accumulated in these regions, the Lac level had no correlation with slow wave magnetic activity.

Figure 6 shows isocontourlines of the spatial distribution of the abnormal slow waves, the Lac and the NA activities of a patient with a brain infarct. Figure 7 shows an example of the same patient with the topographic development of the three activities (MSI, NA, Lac) along a line from normal to pathological tissue. It appears that the abnormal activity starts relatively far away from the infarct, typically 3 cm or more. [16].

3.2.4.2 Brain tumors: We also compared 7 patients with common invasive and non invasive brain tumors (i.e. astrocytic tumor and menigeoma) to 10 healthy subjects [15]. The protocol was the same as in the infarct study.

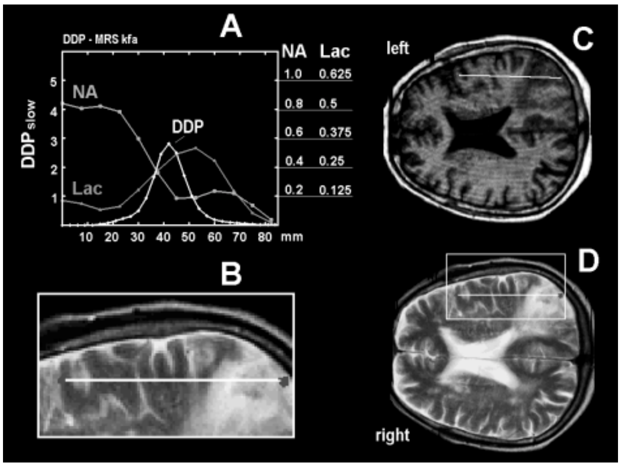

Figure 7: *Intensity of abnormal spontaneous slow wave (2-6 Hz) activity, lactate (Lac) ^{1}H MRSI activity, and N-acetyl (NA) ^{1}H MRSI activity of the same patient (kfa) as in figure 6 (left brain infarct) along a line from normal tissue into the bulk of the brain infarct. Same recording protocol as in figure 6. C: line seen in a T1 image. D: line seen in a T2. Enclosure in a white rectangular line marks the enlarged area in B. The line in B is in direct spatial relation to the three different activities in A. Details in [16] (from [37]).*

Focally increased slow (and fast) wave activities and epileptic spikes were observed in the neuronal area adjacent to the bulk of the tumor with a mild reduction of NA and a slight accumulation of Lac. Lac intensity was less pronounced than in the infarct study. The bulk of the tumors was magnetically silent. The extension of the tumor border zone seems to depend on the invasiveness of the tumor, but it seems to be smaller than that of the infarcts, typically about 2 cm. Figure 8 shows an example of the intensity of the three activities along a line from tissue of the border zone of a tumor through the tumor and back to tissue outside the tumor again [15].

3.2.4.3 Consequences: From the results of both studies we could assume, that preserved and metabolically active cortical tissue in the border region of infarcts and tumors with remaining NA signal and the increased slow wave activity under lactic acidosis (mild accumulation of Lac) could be one of the ischemic "penumbra" states [15,16]. So slow wave sources can serve as a marker to localize the penumbra of infarcts and tumors. The clinical importance is to have a diagnostic tool to find and followup areas of neurons, where in the case of infarcts therapeutic measures (i.e. neuroprotectors) might prevent neurons to be damaged irreversibly. In the case of tumors an early detection of prestages of tumors can be possible.

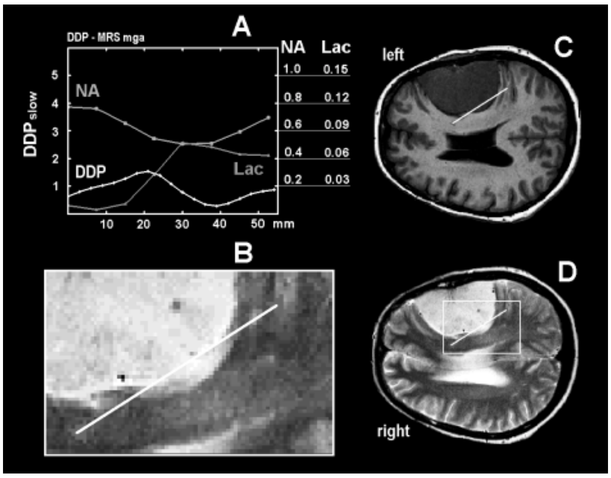

Figure 8: *Intensity of abnormal spontaneous slow wave (2-6 Hz) activity, lactate (Lac) ^{1}H MRSI activity, and of N-acetyl (NA) ^{1}H MRSI activity of a 53 years old female (mga) with a left meningeoma along a line from tissue in the border zone through one pole of the tumor and back to border zone tissue on the other side of the meningeoma. Same recording protocol as in figures 6 and 7. C: line seen in a T1 image. D: line seen in a T2. Enclosure in a white rectangular line marks the enlarged area in B. The line in B is in direct spatial relation to the three different activities in A. Details in [15,16] (from [37]).*

4 Conclusions

In our studies we could demonstrate: the localization of the function of eloquent cortical areas is well accepted in functional image guided neurosurgery. The localization of the epileptogenic lesion is an additional promising tool in the presurgical investigation of epileptic patients. The penumbra of transient ischemic attacks (TIAs), of infarcts and of tumors can be localized. A possible screening for "asymptomatic TIAs" (clinically silent reversible neuronal deficit) might help in the prevention of strokes. In patients with infarcts the knowledge of the localization and the extent of the penumbra may serve as a basis to prevent the increase of irreversibly damaged tissue. In patients with tumors the localization of the border zone activity may serve as a tool of early detection or prestages of tumors. More clinical studies have to verify the value of these promising tools.

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